“ANALYSIS OF RISK FACTORS FOR CARCINOMA BREAST IN SOUTH INDIAN WOMEN”

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COLLEGE OF ONCOLOGICAL SCIENCES

CANCER INSTITUTE (W.I.A)

Adyar, Chennai 600 020.

CERTIFICATE

This is to certify that this dissertation on "**ANALYSIS OF RISK FACTORS FOR CARCINOMA BREAST IN SOUTH INDIAN WOMEN"** is a bonafide work done by **Dr.Deepika Nayak,** College of Oncological Science, Cancer Institute (W.I.A) in partial fulfillment of the University rules and regulation for Mch Surgical Oncology (Branch VII) Batch 2011-2014 College of Oncological Sciences, Adyar, Chennai under my overall supervision and guidance, to my satisfaction,

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At the outset, I bow before the lotus feet of almighty God without whom nothing could be possible despite my efforts.

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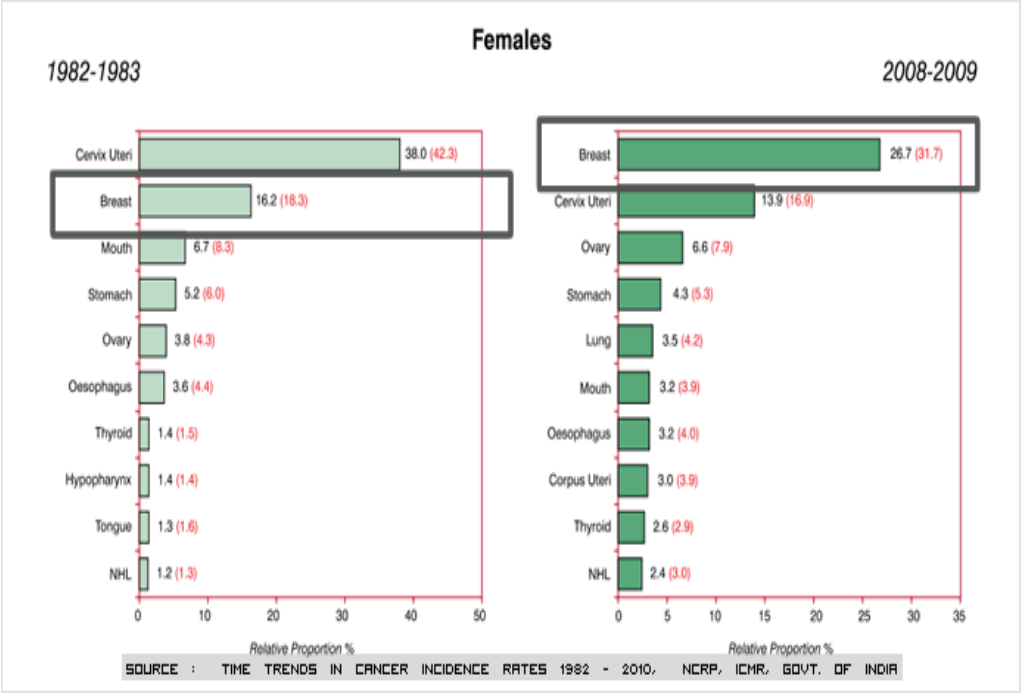
CONTENTS

1. INTRODUCTION

As per National Cancer Registry Programme (NCRP) data, the percentage of breast cancer relative to total cases have increased in South India particularly in Bangalore and Chennai . At present breast cancer accounts for 27% of all cancer in women in Chennai, compared to only 16.2% in 1982.



The survival rates of patients with breast cancer vary significantly between developed and developing countries because of inadequate early detection programmes and lack of necessary

infrastructure for providing treatment in the developing countries.. Coleman et al, reported more than 80% survival from breast cancer in North America and Europe compared with 60% in middle-income countries and 40% in low-income countries (1).

The risk factors for breast cancer are not constant and vary even within in a nation, given that indiviuals follow different life style, religion, customs, habits etc.

Risk factors of breast cancer have been broadly grouped into modifiable and non modifiable .

Modifiable risk factors include those factors a person can control.

Example; weight, BMI, age at first child birth, breast feeding, hormone replacement therapy, socioeconomic status, alcohol consumption, dietary changes with miscellaneous risk factors like night shift work, decreased sleep, abortions etc.

Non modifiable risk factors or fixed factors include age, gender, family history of breast cancer, age at menarche and menopause, exposure to radiation etc.

In this study, an attempt has been made to identify most prevalent risk factors in South Indian women.

2. AIM OF THE STUDY

- To identify the most prevalent risk factors for carcinoma breast in South Indian women.
- To Identify the women at higher risk
- To introduce life style modifications in high risk patients.

Study material utilised :

- Questionnaire.
- Cases of breast cancer.
- Controls included assymtomatic indiviuals from general population and relatives of patients with non hormone dependant cancers.

Study design

- Case- Control study

Study plan

To assess degree of association between individual risk factor and breast cancer with univariate and multivariate analysis and to calculate odds ratio for each risk factor .

3. MATERIAL AND METHODS

Methods:

A few hypotheses that we proposed at the beginning of this thesis included,

1. Breast cancer risk increases with advancing age in South Indian women.
2. Women with an earlier age of menarche and late age at menopause will have a higher risk of breast cancer than women with a later age of menarche and an early menopause.
3. Women with a later age at the first child birth will have a higher breast cancer risk than women with an early age at first child birth.
4. Women with history of abortions will have a higher risk of breast cancer than women with no history of abortions.
5. Women with a higher body mass index will have a higher risk of breast cancer than women with lower body mass index.
6. Women who do moderate exercise regularly have lower risk of developing breast cancer than women who lead a sedentary life.
7. Breast cancer risk is related to the socioeconomic status (income, education and occupation).

8. Women with higher parity have a lesser risk for breast cancer than nulliparous women.

This is a case-control study analysing risk factors of breast cancer. It has been done by recruiting cases from Cancer institute, Adyar and by recruiting controls amongst healthy indiviuals who were either residents of Chennai, or relatives/friends of (nonhormone dependant) cancer patients. Cases and controls were contacted in person. Indiviuals were asked questions to ascertain that the candidates fulfilled the inclusion criteria.

Subjects with any previous treatment history of malignancy were excluded from the study.

Both cases and controls were asked their family history in detail. Indiviuals with history of cancer in family were asked the site of cancer (organ of origin) identified in the family members. In case there was any history of estrogen related cancer within family (such as breast cancer, ovarian cancers, endometrial cancers) those candidates were excluded from the study. Indiviuals with family history of head and neck cancers, blood cancers, gastro inttestinal malignancy etc were included in the study.

Also indiviuals with any history of mental impairments or history of treatment for the same were excluded from this study.

Patients essentially required to have a diagnosis of invasive breast cancer. That is, individuals were not enrolled in the study before knowing their diagnosis. Participants who had a subsequent benign diagnosis or diagnosis of carcinoma in situ were excluded.

Cases included women diagnosed with primary carcinoma of breast. These women had completed treatment in 2013 or were under treatment in 2013 at Cancer institute, (WIA), Chennai.

Participants (both cases and controls) selected for the study were then required to sign a consent form. Illiterate patients were to provide their thumb print.

Study participation was preceded by explaining, the nature of the study and its relevance to the individuals.

All study participants were asked their place of residence. Only women residing in the South Indian states such as Kerala, Tamil nadu, Karnataka, and Andhra Pradesh were included in the study.

Participants were requested to provide their phone numbers for contact regarding any further queries. They were interviewed thereafter with questions pertaining to the questionaire aforementioned .

The questionnaire contained queries relating to name, age, sociodemographic, medical and lifestyle variables, menstrual history, reproductive history, family history of cancer, duration of sleep, as well as potentially carcinogenic environmental and occupational exposures. Please refer to page number 79 for a copy of the questionnaire. Questionaire was discussed with the participants by a doctor or a health care worker. The questionnaire took approximately 10 minutes to complete. Participants were asked to provide their weight and height. The menstrual history and reproductive history were included in the questionnaire. Drug history referring to intake of infertility drugs oral contraceptive pills, and all hormone replacement therapies was also included in the questionnaire. It was also elicited if these drugs were taken recently or previously and if so for what duration. A detailed personal and family history of cancer was included in the questionnaire.

Dietary habits over one's lifetime was categorised into vegetarian or a mixed diet / non vegetarian diet. An occupational history was collected in terms of whether the indiviual was a professional, labourer or employed at any place with risk of exposure

to chemicals. The questionnaire also gathered residential history in terms of urban, rural or semi urban locale of their place of stay.

Candidates were asked what religion they practised and were grouped as Hindus, Muslims and Christians.

Occupational history was elicited. Those who worked as unskilled workers such as Cooli workers or as farm labourers etc were included as labourers. Married women who attended to running their household and not employed per se were grouped as housewives. Indiviuals employed for white collar jobs or as skilled workers (technicians, mechanics etc) were considered as professionals.

Educational qualifications of both cases and controls were enquired about. If the participant did not know how to read and write they were included as illiterates. If the participant had attended school she was asked upto what class she had studied and was then accordingly assessed (primary, secondary, high school). Indiviuals with college degrees were asked if they were graduates or post graduates.

Family income of the individuals was enquired and was broadly grouped as

1. Low income group ie income less than rupees 10,000 per month.
2. Middle income group- rupees 10,000-20,000 per month.
3. High income group- more than rupees 20,000 per month.

Body Mass Index(BMI): Questionnaire asked the subjects their height and weight in metric measurements. BMI was calculated as (weight in kg) / (height in metre)^2.

The BMI categories were as follows:

1) less than 20 kg/m^2, 2) 20.1 -25 kg/m^2, 3) 25-30 kg/m^2 (overweight), 4) 30.1-35 (obese class II), 5)>35 kg/m^2 .

Each individual was asked past history pertaining to any comorbid illness such as diabetes mellitus, hypertension, asthma, tuberculosis etc.

Subjects who had any family history of hormone independent cancer, were asked degree of relation with the relative, site of the cancer and age at diagnosis. In patients with more than one relative having cancer, history pertaining to each relative was asked separately.

Participants were asked the duration of their sleep every night. Patients were particularly asked to mention duration of night sleep

before the diagnosis of cancer was made (to avoid sleeplessness due to anxiety over health issues to be included in the study).

Patients were then asked if they had any prior exposure to radiation either accidental or for treatment of any benign conditions (acne, thyrotoxicosis etc).

Age at menarche was asked to all subjects. They were then enquired if they were still menstruating. If they were still menstruating they were categorised as premenopausal. If not menstruating for more than 6 months they were labelled as post menopausal and age at which they attained menopause was asked for. Post menopausal women were asked if they had any exposure to harmone replacement therapy.

Women with history of hysterectomy were included in post menopausal group with date of hysterectomy being taken as age at which menopause was attained, (unless patient was already post menopausal before hysterectomy, in which case time of cessation of menstual periods was used to decide upon the age at menopause). In most of the women the ovaries were removed during hysterectomy.

Women were asked about number of children they had and age at first child birth. Breast feeding details including duration of the

feeding was collected. Women were also asked if there was any history of abortions. Abortions if any were classified into spontaneous abortions and induced abortions Women who had no children were included in the category of nulliparous individuals.

Subjects were asked life style questions like history of alcohol intake, smoking, use of antiperspirants, daily exercise routine etc.

If the participant was a nonsmoker, she was asked if any other member of the family smoked. If yes, then number of cigarettes/beedis smoked by the family member, per day was asked, in an attempt to understand if subject had any exposure to second hand smoking. Participants were asked to recall the approximate number of hours each week, that the she was exposed to cigarrrette/beedi smoke. The answer to this was generally not very forthcoming.

Statistical analysis: All statistical analyses in this project were done with Microsoft office excel 2007. A series of multiple logistic regression analysis was performed for each of these risk factors. Thereafter, Odds ratios were estimated to calculate the relative risk of each factor being studied.

4. REVIEW OF LITERATURE

DEVELOPMENT OF BREAST

Breasts are modified sweat glands which develop along the milk ridge from 5th week to 8th month of intrauterine life.

Breasts are rudimentary in males and have no functionality.

Throughout the life of a female, breast tissue undergoes a series of changes.

In females, after puberty the glandular elements in the breast develop and the fat deposits increase.

During pregnancy and lactation, the amount of glandular tissue and their functional activity increases.

After menopause, the mammary gland undergoes involution and glandular elements are replaced by fat and connective tissue.

BREAST CANCER TUMOURIGENESIS

Carcinomatous changes can occur due to increased expression of oncogenes (e.g., c-myc, c-ras, c-erb-B2), decreased expression of tumour suppressor genes (e.g., p53, RB), and alterations in cell

structure. Alterations of cell structure leads to loss of cell adhesion, increased expression of cellular proteins (e.g., cyclins, Ki-67), increased expression of angiogenic factors (e.g.,VEGF), and enhanced expression of proteases (e.g., cathepsin-D)(2,3). However these genetic alterations neither manifest simultaneously nor in an orderly progression, but occur in varying combinations in each cancer.

It should also be noted that these genetic and cellular alterations can be found in both invasive and in-situ breast tumours. It is therefore unclear which specific changes create the conditions necessary for stromal invasion and metastasis.

These changes are likely to be initiated by factors such as dietary factors, ionising irradiation and alcohol consumption. Subsequent promotional factors include exposure to oestrogens during reproductive changes.

Approximately 5% of breast cancers are due to inherited genetic mutations of BRCA1 and BRCA2, but the individuals with these inherited mutations have 66-80% risk of developing the disease.

Breast cancer tumorigenesis begins with the loss of regulation of the cell number.

In general the development of breast carcinoma occurs in following stages:

1. Unfolded lobules and usual ductal hyperplasia
2. Atypical ductal hyperplasia
3. Lobular carcinoma -in- situ
4. Ductal carcinoma- in- situ

Unfolded lobules and ductal hyperplasia were thought to cause a 1.5 to 2 fold increased risk, atypical ductal hyperplasia portends a four fold increased risk, lobular carcinoma about a six to ten fold increase in risk and ductal carcinoma in situ about an eight to ten fold increase in risk (25). Lobular neoplasia covers the spectrum from minimal lobular involvement to maximum distention of acini in several lobules.

Risk factors that have been implicated in causation of breast cancer are:

- Age
- Gender
- Lifestyle
- Dietary intake
- Reproductive factors
- Genetics
- Radiation Exposure
- Environmental exposure to carcinogens

Relative Risk <2	Relative Risk 2-4	Relative Risk >4
Early Menarche	One first degree relative with breast cancer	Mutation BRCA1 or BRCA2
Late menopause		LCIS
Nulliparity	CHEK2 mutation	Atypical hyperplasia
Estrogen plus progesterone	Age>35 years at first birth.	Radiation exposure before 40.
Hormone Replacement Therapy	Proliferative breast disease	
Alcohol use Postmenopausal obesity	Mammographic breast density	

Detection of breast cancer in the early stages is key to achieving successful outcome in terms of survival. Early identification of carcinoma breast is possible by isolating patients at high risk, and screening them regularly.

Hence the need to understand interplay between risk factors and need for statistical models.

Most popular risk assessment models for breast cancer are the Gail model and the Claus model.

The Gail model was arrived at from the data generated by a case control subset of Breast Cancer Detection and Demonstration Project.(4,5,6).

Risk factor components of the Gail model include

- age of the person at the time of counseling,
- age at which she attained menarche ,
- age at first live child birth,
- prior breast biopsies if any,
- and first-degree relatives having history of breast cancer.

The Gail model was modified for selecting eligible candidates for National Surgical Adjuvant Breast Project (NSABP) chemoprevention trials. The modifications accounted for risk related to history of atypical hyperplasia and included adjustments to predict risk in African American women(5).

Women aged 35 years and older with 5-year risk of at least 1.7%. were deemed eligible to participate in the NSABP-P1 trial.

Model accuracy for predicting number of breast cancers detected has been validated in studies of screened Texas women, the Nurses' Health Study, and the placebo arm of the NSABP's first Breast Cancer Prevention Trial (BCPT).

National Cancer Institute http://www.cancer.gov/bcrisktool/Default.as

- Amongst the risk factors ,age and gender have the strongest association with breast carcinoma.

  Genderwise women have 100 fold increased risk of breast cancer than men(8).

Age:

There is a steep increase in the incidence rates of breast cancer with age upto of 45 - 50 years, there after the increase in risk is less steep(7). This change in the risk escalation is probably due impact of hormonal change (menopause) that occurs around this time. At the age of 75 to 80 years, the curve has plateaued and the risk begins to decrease thereafter.(4)

Socioeconomic status

Women from affluent society have a twofold increase in risk. This is thought to be because women of higher socioeconomic strata tend to delay child birth, and are more likely to have high calorie diet intake. However they tend to present early as they have a greater awareness of breast cancer and are willing for screening periodically or approach for treatment early. (9)

Also higher levels of education in these women encourage them to be self reliant and to remain single or marry late thereby increasing their risk of breast cancer(15.9% in Indian women). (64,65)

Residence

According to Rajesh Dikshit et al, "In women, there was no difference between breast cancer mortality in rural and urban India. Breast cancer gets diagnosed earlier in urban women than in rural women and hence tend to have a better prognosis. As per the urban cancer registries there has been an increase in incidence of breast cancer of <1% per year between 1991-2005, and an increase in presentation as localized breast cancer" (10).

Early age at menarche

With every two-year delay in the commencement of menarche, there is a 10 % reduction in the risk of beast cancer. A five year delay in menarche caused a 22% reduction in the risk of breast cancer.(11,12) Average age of menarche in developed countries has come down from 16-17 years in the 1850's to 12-13 years today. Good nutrition in early life with increased intake of meat has caused this change in age of menarche. In one case control study of disease-concordant monozygotic twins, the twin with earlier onset of menses was five times more likely to be diagnosed with breast cancer earlier than the other(13).

As per the “Estrogen window hypothesis” , in females with early menarche, there are more number of anovulatory cycles with unopposed production of estrogen. Hence early menarche is associated with increased risk of breast cancer. However with recent studies demonstrating early ovulation after early menarche other theories are being considered. Such theories include : 1) high concentration of progesterone hormone in association with normal or high concentration of estrogen at puberty causes increased risk 2) it is relatively high estrogen concentrations in early life which act as risk factor or 3) the estrogen to androgen ratio is critical, with androgens having a protective role.

Delayed menopause is a risk factor for breast cancer . Every 1-year of delay in the onset of menopause causes a 3% increase in risk of developing breast cancer.(11)

Menstrual patterns/infertility — influence the number of ovulatory cycles over entire life time and alter a woman's extent of estrogen exposure (14).

Pregnancy:

Parity — Nulliparity is associated with relative risk of 1.2 to 1.7. A single child birth can decrease the risk of breast cancer and the

beneficial effect is proportional to the number of children a woman gives birth to.Each child birth reduces the risk of breast cancer by 7%. This protective effect per childbirth is more when the births are at younger ages , i.e a single child birth before the age of 20 years can lower the risk by 30% compared to women with first child birth after the age of 35 years.(15)

Pregnancy exerts a protective effect on breasts. Enigmatically, the risk for breast cancer increases transiently after a term pregnancy. The cause of this phenomenon, is not fully understood.

Age at first birth — The lesser a woman's age at her first child birth, the lower her risk of developing breast cancer . A later age at first birth would mean proliferative stimulation of breast cells that have been exposed to carcinogens and are therefore more prone to cell damage.

In the Nurses' Health Study, the aggregate incidence of breast cancer to the age of 70 years for parous women and age at first child birth was compared to that in nulliparous women.

The data revealed a 20 percent lower risk in parous women if the first birth was at age of 20 years, 10 % lower risk for first birth at age of 25 years, and 5 % higher risk if the first birth was at the age of 35

years. The risk for a nulliparous woman was same as that of a woman with a first full term child birth by the age of 30 years.(15,54)

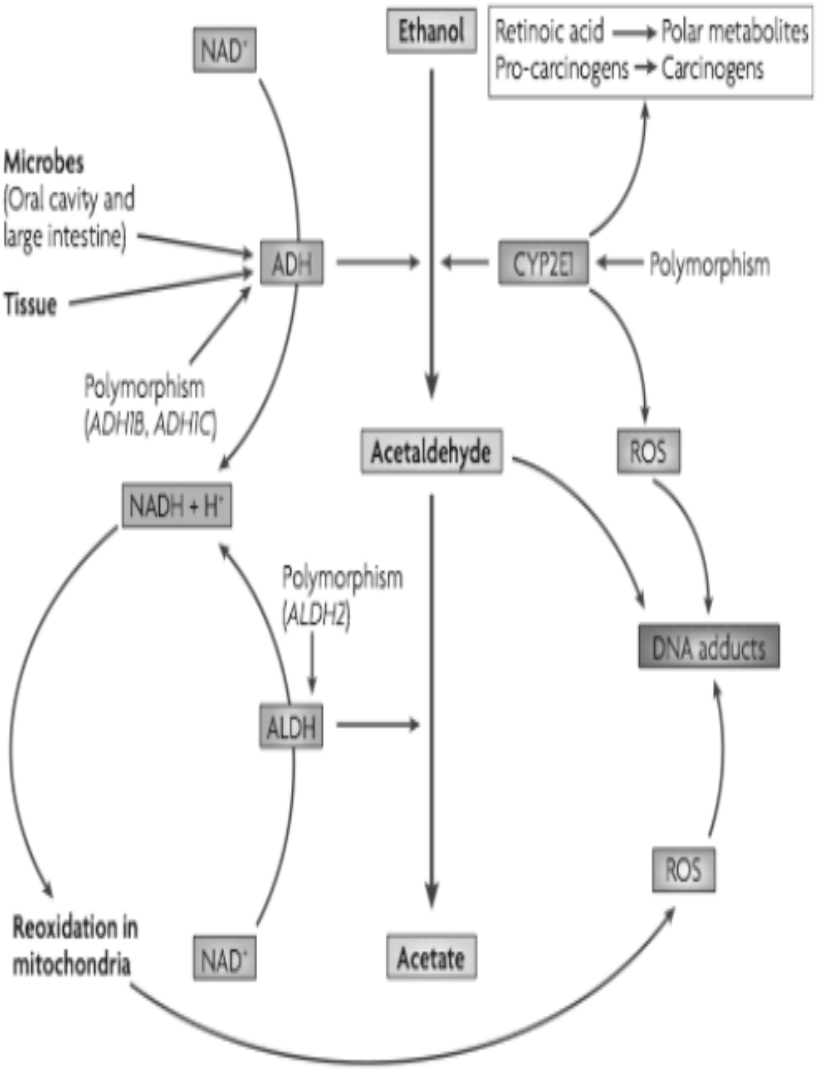
Diet:

The Nurses' Health Study, which commenced in 1976, comprised of 121,700 U.S. registered female nurses between the age group of 30 to 55 years at baseline with 20 years of follow-up.(17)During this period over 3,500 postmenopausal women developed breast cancer. Diet intake of the premenopausal women was obtained at 2- to 4-year interval. It was observed that women with higher intake of animal fat had a 50% greater risk of breast cancer. However no such increase in risk was seen with intake of vegetable based fat. This implies that diet rich in animal fats ,rather than vegetable fat, is the dietary risk factor for development of breast cancer. The significance of this risk factor was more when the animal fat rich diet was taken in the early life.(35)

Alcohol:

As per Seitz and Stickel from 2007 alcohol is oxidised to acetaldehyde by alcohol dehydrogenase (ADH) (CYP2E1) and further metabolised to acetic acid by acetaldehyde dehydrogenase (ALDH).(18)

Acetaldehyde intercalates into the DNA double helix, forming stable DNA adducts.(19) Also CYP2E1 activity generates oxygen free radicals in addition to the acetaldehyde, which themselves react with lipids to form lipid peroxide products which then form more adducts with DNA. The oxidation of ethanol by ADH requires the reduction of nicotinamide adenine dinucleotide (NAD+) to NADH. This process is reversed (i.e., oxidation of NADH to NAD+) within the mitochondria, where more oxygen free radicals are generated(19,20). Also CYP2E1 also decreases tissue levels of retinoic acid, which is an important mediator of cell growth and differentiation. Lastly, CYP2E1 participates in the conversion of procarcinogens (such as para amino hippuric acid) into carcinogens.



ADH	Alcohol dehydrogenace
ALDH	acetaldehyde dehydrogenenase
ROS	Reactive oxygen species.

A more recent (2002) pooled analysis by Hamajima et al. concluded that with every 10g/day increase in alcohol consumption breast cancer risk increases by 7.1% (std. error: 1.3%) .(20)

As per the Million Women Study, of the 1,280,296 women in the United Kingdom who were routinely followed for incident cancer, each alcoholic drink (10g) contributed upto 11 breast cancer cases per thousand women, up to age 75 years.(21)

Hormone Replacement Therapy(HRT)

Hormone replacement therapy is linked to breast cancer, regardless of the hormone type (estrogen or estrogen plus progesterone). Prolonged usage is associated with the highest risk. However , short-term use of combined estrogen-progestin therapy (less than three years in previous users of estrogen) appears not to increase the risk of breast cancer significantly.

In the Million Women Study, there was an increase of up to three percent per year in the risk of breast cancer amongst women taking estrogens replacement therapy. (22,24,26,27)

The Womens health initiative(WHI) was a set of clinical trials and an observational study, run for 15 years. It included a total of

161,808 healthy postmenopausal women. Results from a randomized clinical trial performed within the WHI suggest that postmenopausal women taking estrogen plus progestin experience a five to six percent increase in breast cancer risk per year of hormone replacement therapy(23).

Mechanism of Carcinogenesis of HRT.

Steroid estrogens are metabolised to catechol products. Redox cycling of these catechol metabolites causes oxidative stress and damage to DNA molecules.

BMI AND PHYSICAL ACTIVITY

Studies have found that breast cancer risk decreases by 15% - 50% among women who are physically active. In the California Teachers Study (CTS), a large prospective cohort study of public school teachers, Dallal et al. the degree of physical activity was inversely related to risk of breast cancer(both invasive and in situ types).

In a multicentric study from South India by Gajalakshmi et al conducted at Regional Cancer centre in Thiruvananthapuram, urban women were found to have a relatively larger body size even at a

younger age(47). A direct correlation was observed between breast cancer risk and higher values of anthropometric measurements irrespective of their residence (urban/rural)or their menopausal status.

Obesity is also a risk factor for breast cancer. Overweight premenopausal women, have 10% to 30% decrease in risk of breast cancer than normal weight or leaner women (those with a BMI lesser than 25 kg/m^2).(28) Paradoxically, obesity and adult weight gain are associated with increased breast cancer risk in postmenopausal women. There exists a relative risk of 1.5 to 2.0 when comparing the most obese women or those with the largest weight gain to normal weight women or those with the least weight.

Increase in body weight has opposite effects in terms of risk of breast cancer in postmenopausal and premenopausal women.(29,30)

Postmenopausal breast cancer — obesity in post menopausal women or postmenopausal weight gain are at greater risk of breast cancer in multiple studies. The influence of weight is strongest in women who do not use hormone therapy.

In the US, an analysis of seven prospective studies was conducted. Women who weighed more than 80 kg were at 25% greater risk of breast cancer than women weighing less than 60 kg ie

in terms of body mass index(BMI), women whose BMI exceeded 33 kg/m2 had a 27 % increase in breast cancer risk in comparison to those with a BMI less than 21 kg/m^2.

The levels of oestrogen in tissues is regulated not only by the amount of hormone produced in the body and concentrations in the circulation but also by the levels of sex-hormone-binding globulin (SHBG) bound estrogen(32). Therefore, higher the amount of SHBG ,lesser the levels of free oestradiol that can enter the cells. Lower levels of SHBG is observed in obese women. Also post menopausal women have lower levels of SHBG.Hence levels of estrogen in these women is higher.

The defining biological event of the menopause is the cessation of ovarian hormone production. In postmenopausal women estrogen is produced in peripheral fat by the process of aromatization of androstenedione to estrone(31).Thus, overweight postmenopausal women have increase in levels of circulating estrogen. In premenopausal women, obesity is associated with menstrual disturbances, including anovulatory cycles and secondary amenorrhea, thereby lowering their exposure to estradiol.

Height —Taller women, be it premenopausal or post menopausal ,have higher risk of breast cancer . (30).This was been elucidated in the previously mentioned pooled analysis of seven prospective cohort studies. Women who were more than 175 cm tall had 20 % increase in risk of breast cancer than women who were lesser than 160 cm tall .

Physical activity may act through altering menstrual cycle patterns and hormone profiles both premenopausally and post menopausally. Physical activity in youth lower body fat and delays the relative age when first menses occurs. Physical activity decreases the occurrence of ovulatory cycles in young women. Physical activity also reduces oxidative stress and increases capacity to repair DNA mutations.(33,34)

Cigarette smoking

Smoking induces DNA adducts and p53 mutations in the breast tissues and increases risk of breast cancer.

A pooled analysis by Ambrosone et al demonstrated an increased risk of breast cancer in women with the slow acetylation genotype for N-acetyl transferace 2 (NAT2). This study was based on data from 11,030 women over 9 separate casecontrol studies. Smoking

has been shown to have a modest association with breast cancer risk but the association is only consistent in the NAT2 slow acetylation genotype.(38)

Of seven studies (a mix of case-control and cohort), carried out between 1994 and 2002, that examined passive smoking and breast cancer, five found a statistically significant association. Probably because second-hand smoke contains a higher concentration of PAHs, nitrosamines, and other carcinogenic constituents when compared to the smoke that is actively inhaled by the smoker. (37)

Breast feeding:

The nulliparous women who never breast feed have increased risk of breast cancer. In a case control study by Gajalakshmi et al increased duration of breast feeding was associated with decrease in breast cancer in premenopausal women. In another case control study conducted at Nagpur Government medical college, (59)mothers who never breastfed were at increased risk of developing breast cancer than those who breast-feed their children. (O.R.=1.71, CI=0.54-5.35, $P<0.001$). Also as the duration of breast-feeding increases, risk of breast cancer decreases. (59)

Religion:

In a study in Chennai, breast cancer incidence rates were highest in Christians followed by Hindus and Muslims . Similar results have been reported from a study performed in the South Indian city of Thiruvananthapuram (56).

Family history

In an Indian study on 226 breast cancer patients, 20.7% had a positive family history (57). However there are several studies have shown lesser incidence of familial breast cancer in India. At SGPGIMS Lucknow, only 5% of patients had definite family history of breast and/or ovarian cancer in first degree relatives.

Abortions

Benefits of pregnancy and lactation are achieved in the 3rd trimester when the maturation of breast tissue occurs. As per the 'Abortion-breast cancer hypothesis', if a pregnancy is terminated prior to this maturation of breast tissue, it could have an adverse effect by leaving behind immature cells within the breast which are susceptible to effects of carcinogens and estrogen.(39,40,41,42)

The lobules within the breast are of four types:

Type 1 (undifferentiated immature lobules) are composed of

i)Estrogen-receptor negative (ER-)highly proliferating cells

ii) ER positive (ER+)nonproliferating cells ,

iii)very few ER+ cells that proliferate

Type 2 has 47 ductules (immature)

Type 3 has 80 ductules (mature, with lesser expression of estrogen receptors)

Type 4 are fully matured cells (cancer resistant) .

During early pregnancy, type 1 lobules transforms into type 2 lobules because of the estrogen and progesterone levels. Transformation into type 3 and the fully differentiated type 4 lobules requires human placental lactogen (hPL) which is secreted the last few months of pregnancy. Hence the abortion-breast cancer hypothesis states that if an abortion were to interrupt this sequence then there would bemore number of type 2 lobules than in the prepregnancy period.

However Bernstein *et al.* reported a reduction in breast cancer risk in women injected with hCG for weight loss or infertility treatment.

Contrary to the Abortion breast cancer hypotheses, Michaels *et al.* hypothesize that since hCG causes cellular differentiation and may activate apoptosis, as high levels of hCG are present even early on in pregnancy, "even in the event of an abortion,hCG levels impart the protective benefits of a full-term pregnancy".

The review of the available evidence is "inconclusive" regarding association between abortion and breast cancer.

Hence abortions are considered to be controversial risk factor for ca breast.

Although some studies suggest a slightly increased risk of breast cancer in postmenopausal women with type 2 diabetes, others do not.

Breast density

Dense breast tissue (defined as ≥75 percent density on mammography) is associated with five times greater risk of breast cancer compared to women of similar age with less or no dense breast tissue.

However there is little understanding of how to quantify the breast density accurately, given that mammography evaluates breast in a two dimension format.

Breast cancer in dense breasts can be estrogen receptor positive or negative. As per a case-control study of postmenopausal women from the Nurses' Health Study breast density was independent of estrogen related effects.

EXPOSURE TO IONIZING RADIATION — Exposure to ionizing radiation as in treatment of Hodgkins lymphoma(Mantle field radiation) or in survivors of nuclear disasters ,is associated with an increased risk of breast cancer . The prepubertal girls are most vulnerable to effects of radiation.(36,37,38)

As per the Cornell University' s website (2005) which studied radiation-induced breast cancer ; young women are more susceptible than older women ,and would develop breast cancer about 5-10 years after exposure to radiation.

ENVIRONMENTAL EXPOSURES - Digoxins, and organochlorine pesticides such as DDT(43,44,45,47) are weak estrogens, highly lipophilic, and persist within the body for years. However, many large studies have failed to show such an association.

Nocturnal light exposure/Night shift work — By definition ,night shift work includes schedule that included overnight work which induces circadian rhythm disturbances.

A meta-analysis which included 13 reported studies of airline cabin attendants and night time shift workers, studied the relationship between night work and breast cancer risk (48,49).

As per the study, exposure to light at night suppresses the normal nocturnal production of melatonin by the pineal gland, and increases the risk of breast cancer. This has been confirmed by an inverse association between urinary levels of 6-sulfatoxymelatonin (the major melatonin metabolite) and the risk of breast cancer. In addition, in women who did not typically sleep between 1 AM and 2 AM, the night time period when melatonin levels are at their highest (OR 1.14), the risk of breast cancer was highest (48,49).

Hypotheses to explain the oncostatic action of melatonin include the hormone's antimitotic effects and limited antioxidant activity and control of cellcycle through the p53–p21 pathway. Finally, several clinical trials confirm the protective role of melatonin, either alone or in combination with standard therapy regimens in several human cancers.

Risk modification

Few data address the benefit of risk factor modification in breast cancer. In a large case-control study of invasive breast cancer in women from six Italian regions, and breast cancer incidence and mortality data from the Florence cancer registries, investigators attempted to incorporate three modifiable risk factors (alcohol consumption, physical activity, body mass index [BMI]) into a breast cancer prediction model, estimating the potential risk reduction that might result from optimization of the risk profile: no alcohol consumption, exercise at least two hours weekly, and maintain BMI <25 kg/m^2 after the age of 50. The mean relative breast cancer risk reductions over 10 -20years by optimizing modifiable risk factors was in the range of 20 to 25 percent, which translated into reduced absolute risk of 0.6 to 4.4 percent, depending upon the risk group.

Chemoprevention — For women at higher than average risk, risk of developing breast cancer can be reduced by 50 percent or more by taking tamoxifen or raloxifene for five years. Tamoxifen and raloxifene are both approved by the United States Food and Drug Administration (FDA) for the prevention of breast cancer. The common side effects of tamoxifen include, hot flushes, menstrual irregularities, vaginal discharge, but the uncommon serious ones

include blood clots, pulmonary embolus, stroke and uterine cancer particularly in women over 50 years of age. Raloxifene is approved in post menopausal women and has a lower risk of thromboembolic events, and uterine cancer compared to tamoxifen.

In women at high risk for developing the disease, the risk of death from breast cancer can be reduced by regular screening mammogram.

As per study conducted in urban Delhi, amongst 56% women who were aware about breast cancer; 51% knew about at least one of the signs/symptoms, 53% were aware that breast cancer can be detected early, and only 35% mentioned about risk factors (60). Surprisingly a lower proportion of women (16.4%), who claimed to be familiar with BSE, but none of them ever practiced it; 6/342 (11%) had received some form of training from a local NGO and the rest had sourced their knowledge from either the television or the print media (61).

In rural Kashmir only 4% of the women had received any training or education about the purpose and technique of breast self exam (62). Since self detection remains a key method of breast cancer

through the world even now, it is logical that the women in India should be made breast cancer aware (63).

5. Study Materials

As such, 195 cases and 196 controls participated in the study.

Cases were newly diagnosed, histopathologically confirmed invasive breast cancers registered in Cancer Institute in 2013.Controls were women randomly selected from population of apparently healthy individuals during the same period. Subjects of the study were of age ranging from 18 to 85 years.

Methods and Statistical analysis

Summary descriptive statistics and frequencies for known breast cancer risk factors were studied between cases and controls.

Odds ratios were used as estimates of relative risk along with 95% confidence intervals were reported.

To achieve the objectives of the current project, a series of bivariate logistic regression analyses (univariate and multivariate) were performed in order to ascertain associations between the numerous exposures of interest and breast cancer risk.

Logistic regression analyses were performed on the known and suspected risk factors for breast canncer. Initially, a univariate logistic regression model that was adjusted for age only was created for each of the risk factors. Thereafter, a multivariate analysis of all factors that emerged significant was performed.

RESULTS

The following tables illustrate summary statistics and frequencies for breast cancer risk factors analysed across case and control groups. All cases had a diagnosis of breast cancer prior to enrollment in the study and had a histopathologically confirmed malignancy.

Since cases and controls were frequency matched based on age, the average age of the two groups were similar. The case and control groups had mean ages of 55.62years (SD=10.31) and 55.96 years (SD=9.89), respectively. The largest five-year age block was from 50-54 years of age .The more than 70 years age block contained the smallest numbers of participants (with 11 cases and 11 controls).

Table. 1- Distribution of Age amongst cases and controls

Age (Year)	Controls	Cases	Total
<30 Years	12 6.1%	12 6.2%	24 6.1%
30- 39 Years	31 15.8%	31 15.9%	62 15.9%
40-49 Years	56 28.6%	55 28.2%	111 28.4%
50-59 Years	67 34.2%	58 24.6%	115 29.4%
60-69 Years	19 9.7%	38 19.5%	57 14.6%
≥70 Years	11 5.6%	11 5.6%	22 5.6%
Total	196 100.0%	195 100.0%	391 100.0%

Table 2. Distribution of Residential Status amongst cases and controls

Residence	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Rural	29 14.8%	62 32.0%	91 23.3%	1	-	-
Semi Urban	61 31.1%	58 29.4%	119 30.5%	0.445	0.252	0.766
Urban	106 54.1%	75 38.6%	180 46.2%	0.327	0.192	0.556
Total	196 100.0%	195 100.0%	390 100.0%			

Table.2 shows distribution of residential status amongst cases and controls .46.2% of the participants were from the urban areas.The association between residential status and breast cancer was found to be significant (p value of 0.001). The individuals in urban area were found to be at lesser risk than those in rural areas.

Table.3-Distribution of Socio Economic Status amongst cases and controls.

Socio economic code	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Lower	93 47.4%	130 66.7%	223 57.0%	1.00	-	-
Middle	89 45.4%	52 26.7%	141 36.1%	0.418	0.271	0.645
High	14 7.1%	13 6.7%	27 6.9%	0.664	0.296	1.479
Total	196 100.0%	195 100.0%	391 100.0%			

Table.3 shows association between breast cancer and socioeconomic status(p value = 0.001). The majority of participants belonged to the lower socioeconomic strata (57%).

Table.4- Distribution of Occupational Status amongst cases and controls.

Occupation	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Labourers	39 19.9%	54 27.7%	93 23.8%	1.00	-	-
House Wives	120 61.2%	115 59.0%	235 60.1%	0.692	0.426	1.124
Professionals	37 18.9%	36 13.3%)	63 16.1%	0.664	0.296	1.479
Total	196 100.0%	195 100.0%	391 100.0%			

Table .4 shows association between breast cancer and occupation

p value = .108 (not significant).

Table.5- Distribution of Body Mass Index (BMI) amongst cases and controls

BMI (Kg/m2)	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
<25	105 53.5%	96 49.2%	201 51.4%	1	-	-
25.01 – 30	63 32.1%	70 35.9%	133 34.0%	2.667	1.183	6.009
>30	28 14.3%	29 14.9%	57 14.6%	4.800	0.999	23.072
Total	196 100.0%	195 100.0%	391 100.0%			

Table. 5 shows that association between classified BMI and breast cancer .The p value for this association was 0.022(significant). Women with BMI> 30kg/m2 were at greater risk of developing breast cancer than women with BMI<25kg/m2.

Table.6 -Distribution of Dietary habits amongst cases and controls.

Diet	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Vegetarian	73 37.2%	52 26.7%	125 32.0%	1.00	-	-
Non-Vegetarian	123 62.8%	143 73.3%	266 68.0%	1.632	1.062	2.500
Total	196 100.0%	195 100.0%	391 100.0%			

Table.6 shows association between dietary intake and risk of breast cancer. Dietary intake was classified into non vegetarian / mixed diet and pure vegetarian diet. The association between diet and breast cancer was found to be significant (p value = 0.02). Non vegetarian diet was found to be a risk factor for breast cancer (OR = 1.632)with 63% increased risk compared to vegetarian diet.

Table.7-Distribution of Physical activity amongst cases and controls.

Physical activity	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Mild	146 78.1%	171 87.7%	307 80.6%	1.00	-	-
Moderate	50 21.9%	24 12.3%	74 19.4%	0.392	0.223	0.653
Total	196 100.0%	195 100.0%	381 100.0%			

Table.7 shows association between breast cancer and physical activity. The participants physical activity was classified into mild and moderate activity .19.4% of the participants indulged in some form of exercise in addition to daily routine were included in the moderate physical activity group. The association between physical activity and breast cancer was found to be significant with p value = 0.001. The participants who preferred moderate activity has reduced risk of breast cancer (OR = 0.392.) compared to those with mild physical activity.

Table.8- Distribution of Abortions amongst cases and controls.

Abortions	Controls	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
No	180 91.8%	163 83.6%	343 87.7%	1	-	-
Yes	1.6 8.1%	32 16.4%	48 12.31%	1.656	0.815	3.365
Total	196 100.0%	195 100.0%	391 100.0%			

Table.8 shows association between abortions and breast cancer. 12.31% of the entire study population gave history of abortions. The association between abortions and breast cancer was found to be significant p value = 0.014.

The women who underwent abortions had a greater risk of developing breast cancer (OR = 1.656).

Table.9-Distribution of Age at Menarche amongst cases and controls.

Age at Menarche (Years)	Control	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
<12	34 17.3%	42 21.5%	76 19.4%	1.00	-	-
>13	162 75.7%	153 78.5%	315 80.6%	1.198	0.801	1.792
Total	196 100%	195 100%	391 100%			

Table.9 shows relation between breast cancer and age at menarche. The p value for this association was 0.285 which is not statistically significant.

Table.10-Distribution of Breast Feeding amongst cases and controls.

Breast Feeding	Control	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
No	28 14.3%	27 13.8%	55 14.1%	1.00	-	-
Yes	168 85.7%	168 86.2%	336 85.9%	0.419	0.267	0.656
Total	196 100%	195 100%	391 100%			

Table. 10 shows significant association between breast feeding and breast cancer.p value ≤ 0.05 (significant).There was 59% reduced risk of breast cancer among those who breast fed compared to those who did not.

Table.11-Distribution of Duration of Breast Feeding amongst cases and controls

Duration of Breast Feeding	Control	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
1 Year and below	66 39.3%	96 57.1%	162 48.2%	1.00	-	-
Above 1 year	102 60.7%	72 42.5%	174 51.8%	0.419	0.267	0.656
Total	168 100%	168 100%	336 100%			

Table.11 shows association between duration of breast feeding and breast cancer. In our study, 336 participants gave history of breast feeding. Of these 48.2% participants breast fed for < 1 year and 51.8% breast fed for >1 year.

p value for this association was 0.001 which is significant. The women breast fed for longer time had approximately a 60% reduction in the risk of developing breast cancer.

Table. 12- Distribution of Religion amongst cases and controls

Religion	Control	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Hindu	179 91.3%	166 85.1%	345 88.2%	1.00	-	-
Muslims	6 3.1%	16 8.2%	22 5.6%	2.816	1.099	7.523
Christians	11 5.6%	13 6.7%	23 5.9%	1.176	0.505	2.738
Total	196 100%	195 100%	391 100%			

Table.12 shows, no significant association between religion and breast cancer.

p value for this association was 0.108 (not significant).

Table.13-Distribution of Educational Status amongst cases and controls

Education	Control	Cases	Total	Odds Ratio	95% for Confidence Interval	
					Lower	Upper
Illiterate	18 9.2%	51 26.3%	69 17.7%	1	-	-
Primary	18 9.2%	24 12.4%	42 10.8%	0.471	0.209	1.062
Middle	29 14.8%	46 23.7%	75 19.2%	0.560	0.275	1.139
Secondary	73 37.2%	39 20.1%	112 28.7%	0.189	0.097	0.366
College	58 24.6%	34 17.5%	92 23.6%	0.207	0.104	0.410
Total	196 100%	195 100%	390 100%			

Table. 13 shows significant association between education and breast cancer.

All the factors that were identified as statistically significant in univariate analysis were subjected to multivariate analysis by logistic regression.

Confounders like age at diagnosis and socioeconomic status were adjusted in the analysis .

Table .14 gives the results of final model of multivariate analysis.

Residential status did not emerge as an independent risk factor for breast cancer.Factors like BMI, physical activity and breast feeding emerged as independent risk factors for breast cancer.Five fold risk was forthcoming for those with BMI>33, and 71% reduction in risk for women who breast fed for more than 1 year. And 48% reduced risk for those who had 48% moderate physical activity.

Table .14 -MULTIVARIATE ANALYSIS*

	Odds ratio	95% C.I.for odds ratio	
		Lower	Upper
Duration of breast feeding			
<1 yr	1.000	-	-
>1 year	.297	.172	.512
Residence			
Rural	1.000	-	-
semiurban	1.209	.567	2.580
urban	.659	.320	1.357
BMI			
<20kg/m^2	1.000	-	-
20.01-25	3.367	1.152	9.847
25.01-30	4.049	1.349	12.152
30.01-35	3.534	1.023	12.207
>35.01	5.021	.776	32.484
Physical activity			
Mild	1.000	-	-
Moderate	.520	.277	.978

*Adjusted for age at diagnosis and socioeconomic status.

6. DISCUSSION

This project sought to examine the relationships of a number of risk factors, both known and suspected, with breast cancer risk.

Recommendations have been put forth for adopting new strategies to reduce risk of breast cancer among women.

Breast cancer is a major public health concern. There is a general lack of awareness amongst women about breast cancer .There is also dearth of measures taken to implement prevention ie implement life style changes which can reduce risk of breast cancer.

The frequency matching of cases and controls based on age was done. Hence, influence of age on breast cancer risk in the study population could not be assessed.

A strong association was detected between a number of risk factors and breast cancer in both univariate and multivariate analysis.

In the univariate analysis there was a strong association between breast cancer and risk factors such as duration of breast feeding, history of abortions, degree of physical activity, menopausal status, socioeconomic status and residential areas.

Breast feeding is a very common amongst Indian mothers. However the duration of breast feeding varies amongst these

women..In our study participants were grouped into ones who breast fed for less than a year and those who breast fed for more than a year. The participants who breast fed for more than 1 year were at lesser risk of developing breast cancer as per our study. Women who breast fed for more than 1 year were at 60% lesser risk of developing breast cancer than women who breast fed for less than 1 year.

Physical activity has a protective role against breast cancer. In our study women who performed yoga or went for walks were included in moderate activity. These women were at 60% lesser of developing breast cancer.

Women with BMI more than 30kg/m2 were at 4 times greater risk of developing breast cancer than women with BMI less than 20 kg/m2.

The observation that increase in BMI and physical activity have reverse effects on breast cancer emphasises the need to implement life style changes amongst Indian women. Women must be encouraged to perform some form of exercise in their daily lives. Physical activity acts as an independent protective factor against breast cancer and also exerts protective effect by lowering BMI for obese women.

Abortions are one of the controversial risk factors of breast cancer. The association between history of abortions as studied in the univariate analysis suggested that abortions posed 60% greater risk of developing breast cancer. Hence as per our study abortions do indeed pose increased risk for developing breast cancer.

Both middle and higher socioeconomic strata subjects were shown to be at decreased risk of breast cancer when compared to lower socioeconomic strata. Also women with better education had lesser risk of developing breast cancer.

However, these finding are not consistent with research findings cited previously, which has shown a higher breast cancer risk for women from affluent society and increased levels of education.

Although the reason for this phenomenon is difficult to ascertain from the data at hand, it may be attributed to selection bias in the control group.

This study, had roughly twice the number of middle and higher socioeconomic strata .Also the number of women with education upto secondary level or college were twice in the control group than in the case group. There is a probability that the selection bias contributed to

the findings mentioned before. All the above factors emerged as potential confounders in the study.

Hence in the multifactorial analysis abortion, physical activity, diet, family history, BMI, residence area and breast feed duration were studied.

After adjusting the age and residence factors, the factors that still emerged statistically significant were breast feed duration, BMI and physical activity . An increasing risk of breast cancer with increasing BMI, to the tune of 3-5 folds was observed and was statistically significant. 48% reduced risk of breast cancer was observed among women with moderate exercising compared to minimal category was statistically significant ($p=0.043$). 71% reduced risk of breast cancer was observed for women who breast fed for more than a year compared to those <1year and was statistically significant ($p<0.001$).

This project did not show any association between second hand smoking and breast cancer risk. This could be because many candidates were not able to quantify exposure to second hand smoke in terms duration. Women who had very low levels of exposure were included with zero exposure group. This may comprise a source of misclassification.

Not all known risk factors were shown to be significantly associated with breast cancer risk.

Age at menarche and age at menopause were not associated with risk of breast cancer.

Although these variables are established breast cancer risk factors , the literature has been mixed with respect to age of menarche . That is, not all studies have found these variables to be associated with breast cancer(56)

Further, this thesis study did not support a relationship between breast cancer risk and occupation.

Although it was hypothesized that number of sleep hours and night shift work would be a breast cancer risk, in this study both factors were not significantly associated with risk of breast cancer.

Strength of this study

The main strength of this specific thesis project include the fact that it examined both well-established risk factors and suspected breast cancer risk factors in an attempt to create a comprehensive model that encompasses both genetically related and environmental factors within the south Indian women (study included women from all four south

Indian states, namely Kerala, Karnataka, Andhra Pradesh, Tamil Nadu).

Limitations

Limitations of this study include the potential for selection thesis bias, recall bias, residual confounding, uncertainty regarding latency of exposures.

In order to compensate for selection bias, age was included in all logistic regression models in order to account for the effects of this variable on other associations of interest.

Response bias can also result from cases underreporting exposures because of feelings of guilt .Risk of recall bias is inherent in the use of any tool that relies on subjects' memories of pastevents. However, the administration of a structured and detailed questionnaire to both cases and controls in the study is likely to attenuate the effects of such bias.

7. FUTURE DIRECTIONS

A logical next step would be to extend this research to a sample more South Indian women. Way to accomplish this would be to collaborate with other research groups

Women must be encouraged to have a healthy lifestyle Vegetarian diet, excercises and lowering BMI must be encouraged.

Lactating mothers must be made aware about protective effects of breast feeding for more than 1 year.

Future studies could also consider the addition of analysis of mammographic density. As previously mentioned, there is now a burgeoning line of research that considers mammographic density as a risk factor for breast cancer. While the current study was concerned specifically with breast cancer etiology and thus focused on first occurrence of disease, risk factors for disease recurrence in an area of emerging interest. It would be useful for clinicians to have a readily available tool to predict the chances of recurrence, given a particular set of risk factors. There are already immunohistochemical tools to help predict breast cancer recurrence risk, such as Mammostrat. However, it would be interesting to compare such tools to an

affordable (perhaps even free) regression based prediction tool that simply utilizes data from a patient's medical history.

Breast cancer is a complex disease with many etiological contributors from both nature and nurture. This project is potential step towards the cancer prediction tools .

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Informed consent

I…….. have been explained about the study regarding analysis of risk factors in carcinoma breast in south Indian women. I hereby give consent to participate in this study and have no objection to use of information provided for publications and research purposes.

…… ……

Doctor **Patient / Control**

PROFORMA

NAME: AGE: Place:

Date of interview:

OCCUPATION:

i)labourer

ii)professional)

iii)others

(including chemical factory workers, exposure to pesticides)

Religion

i)hindu

ii)muslim

iii)jains

iv)others

Education i)illiterate ii)school (primary,middle,high school) iii)college(graduate/post graduate)

Residence: i)urban ii)semi urban iii)rural

STAGE OF THE DISEASE:

Weight:

Height:

BMI:

PAST HISTORY: (Any comorbid illness)

(DM/HTN/ASTMATIC/TB/OTHERS)

FAMILY HISTORY:

i)first degree relatives

ii)second degree relative

iii)third degree relative age at diagnosis.

PERSONAL HISTORY:

a)diet

i)vegetarian (Including fried food items,buffalo milk)

ii)non vegetarian

iii)mixed

b)sleep(duration of sleep)

c)night worker

d)h/o intake of OCPs

i)currently

ii)recent

iii)previously

e)h/o HRT

f)parity

g)alcohol consumption

h)use of antiperspirants

Physical activity (i) minimal exercise ii)moderate

iii)sedentary

TREATMENT HISTORY

a) mammographic density

b)h/o prior exposure to radiation

c)previous breast biopsies

d)tobacco consumption

e)smoking

f)h/o hysterectomy

MENSTRUAL HISTORY:

a)age at menarche

b)premenopausal/postmenopausal c) age at menopause

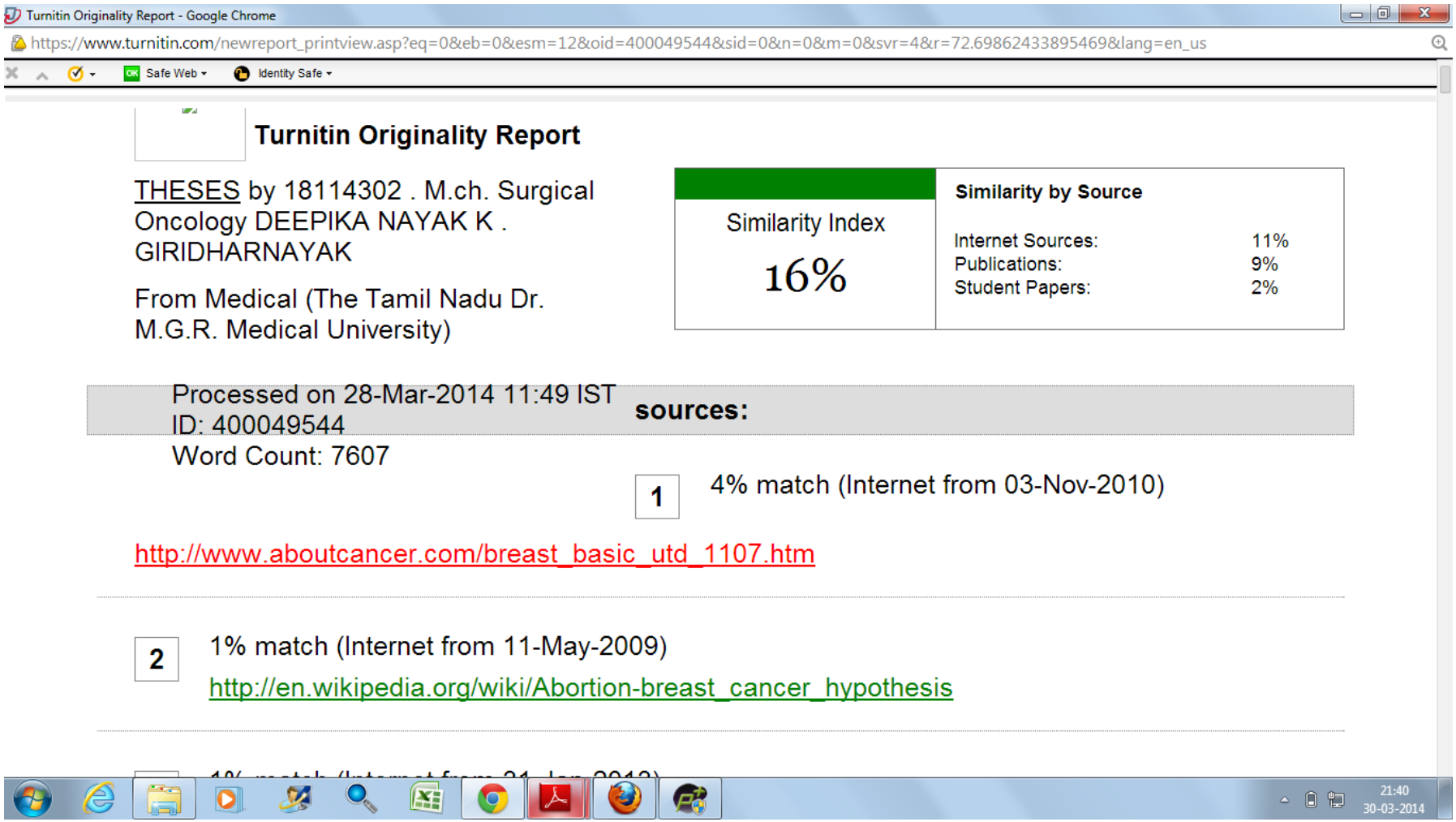
d)history of abortions i)spontaneous ii)induced

e)no. of abortions

Reproductive history: -age at first child birth

breast feeding i)yes

ii)no duration: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